Noninvasive approaches to assessing inflammation

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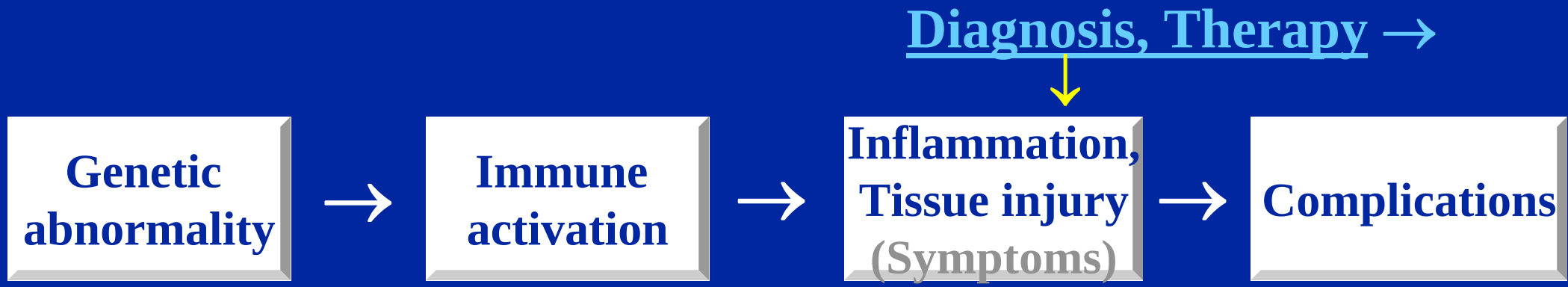
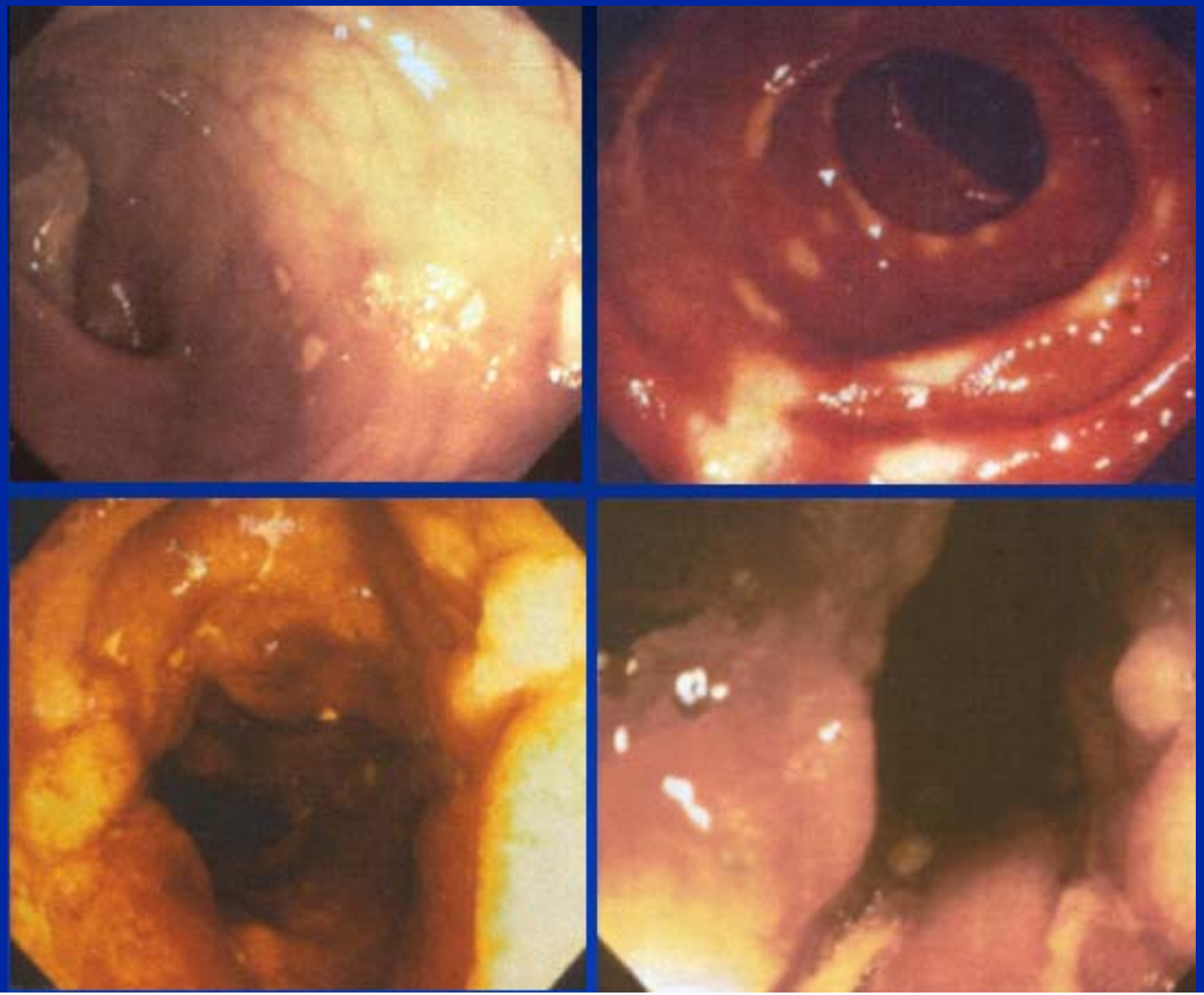
The clinical problem: Inflammation is detected and treated late in its natural history, usually at an irreversible stage



Crohn's:	NOD2	Macro, TH_1	+++	abscess, obstruction
RA:	?	Macro, IgG, TH_1	+++	joint destruction
ANCA:	?	PMN, IgG	+++	renal failure
Athero:	?	Macro, endothelium	+++	arterial blockade
Diabetes	?	Macro, Th1	+++	vasculopathy, renal

Post-Operative Recurrence of Crohn's disease: Endoscopic Grade (Rutgeert's et al)



i1

i2

No Symptoms

i3

i4

Symptoms

The Solution: Diagnose and treat inflammation earlier in its natural history, while at a reversible stage

(Prevent tissue injury and complications)

Diagnose, Induce & Maintain Remission →

Genetic abnormality	→	Immune activation	X	Inflammation, Tissue injury	X	Complications

Crohn's:	NOD2	Macro, TH_1	(-)	abscess, obstruction
RA:	?	Macro, IgG, TH_1	(-)	joint destruction
ANCA:	?	PMN, IgG	(-)	renal failure
Athero:	?	Macro, endothelium	(-)	arterial blockade
Diabetes	?	Macro, Th1	(-)	vasculopathy, renal

Goal of Program

Develop noninvasive means to determine the location and intensity of inflammation in inaccessible organs of patients with various chronic inflammatory diseases.

Strategy: Apply basic knowledge of endothelial/ inflammatory cell interactions, activation of immune cells, vascular permeability and neovascularization to novel imaging techniques

Initial focus: Inflammatory bowel diseases (IBD: Crohn's disease and ulcerative colitis), rheumatoid arthritis, atherosclerosis, and anti-neutrophil cytoplasmic antibody (ANCA)-mediated vasculitis

Potential clinical applications of methods to noninvasively detect inflammation

- **Improved diagnosis:** differential dx, greater acceptance, preclinical detection, localize disease
- **Determine disease activity:** response to treatment, aggressiveness of Rx, identify subsets, distinguish inflammatory vs. functional sx, dx complications
- **Insights into pathophysiology and mechanisms of drug activity:** cell trafficking, cellular interactions, signaling pathways, apoptosis, cells and molecules targeted with treatment

Noninvasive approaches to assessing inflammation

Multidisciplinary, interactive group of >60 investigators from 9 departments, 8 centers, 5 schools, 3 universities and the EPA

Specific aims of P20 grant:

1. **Develop an administrative structure to plan and coordinate activities and promote interactions between investigators**
2. **Organize 1-2 topic-driven workshops each year – local investigators and external experts**
3. **Support pilot studies to develop novel techniques for application to inflammatory disease models**

Leadership of UNC program on Noninvasive approaches to assessing inflammation (1 P20 RR020764)

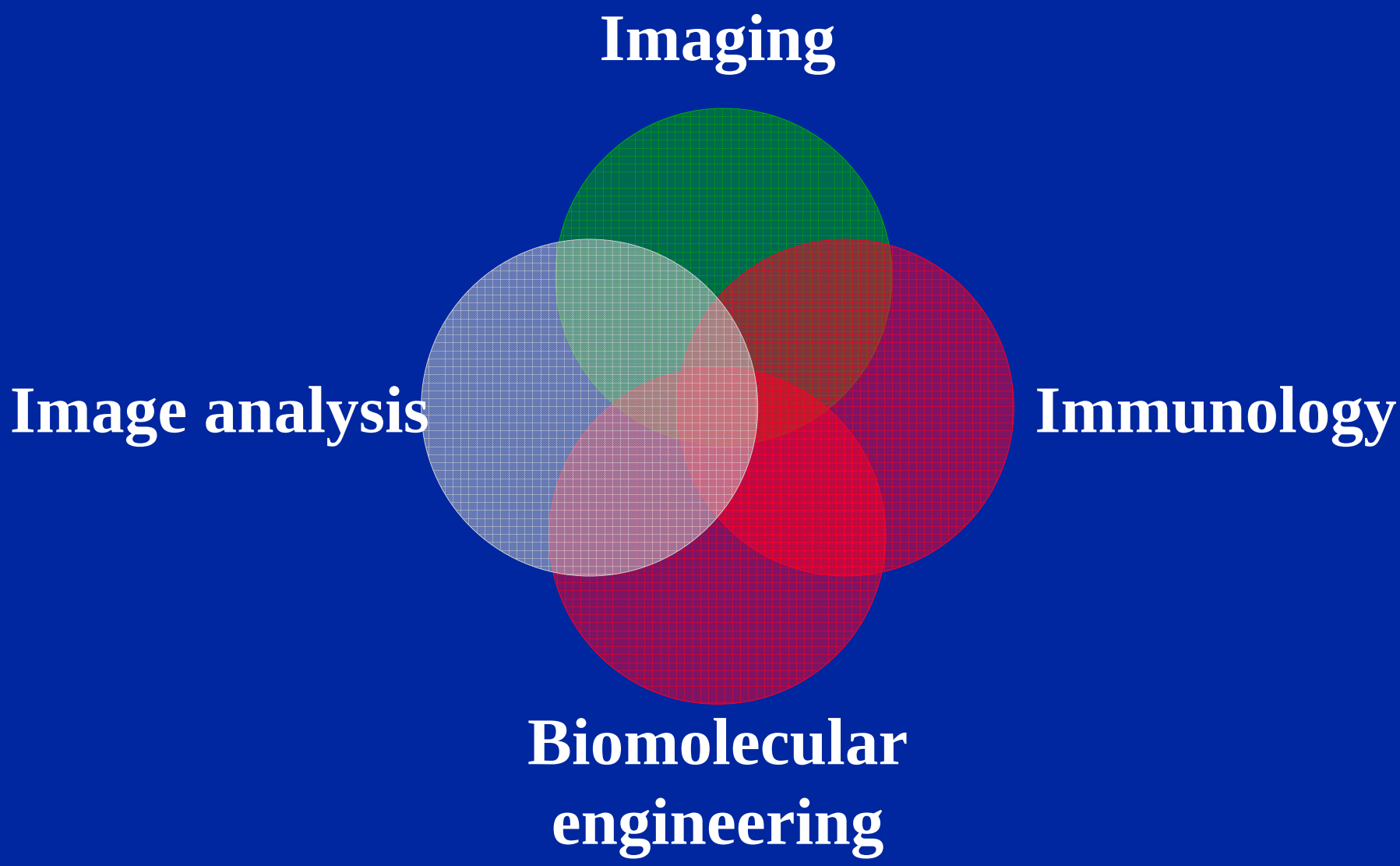
Director: Balfour Sartor, M.D. (Depts. Medicine, Microbiology, Immunology)

Co-Director: Etta Pisano, M.D. (Depts. Radiology, BME)

Executive Committee	Department	Role
Ron Falk, M.D.	Medicine	Chair: Clinical trials
Pat Flood, Ph.D.	Peridont., Micro/Immun.	Member at large
Lester Kwock, Ph.D.	Radiology	Chair: Imaging
Troy Nagle, Ph.D.	BME	Liaison: Bio engineering /Biophysics
Tim Nichols, M.D.	Medicine, Path	Chair: Animal models
Dhaval Patel, M.D., Ph.D.	Medicine, Micro/Immun.	Chair: Basic Science
Steve Pizer, Ph.D	Computer Science	Chair: Image analysis

Coordinator of UNC NIH Roadmap initiatives: Rudi Juliano, Ph.D. Dept. of Pharmacology, Karen Stone, Vice- Chancellor's office

Components of P20 Team



Noninvasive approaches to assessing inflammation

Strategy:

1. **Identify the molecular targets (WBC, endothelial cells) that are selectively increased with inflammation**
2. **Create probes targeting these molecules that can be detected by functional CT, MRI, PET,or Doppler scans**
3. **Validate techniques in animal models of intestinal, rheumatologic, renal , vascular, pulmonary and cerebral inflammation**
4. **Apply to human diseases in pilot studies (IBD, RA, SLE, ANCA+ vasculitis, asthma, graft rejection)**

Opportunities: Pilot/feasibility grants, workshops

Pilot projects

5 projects/year to $50,000, 1 year duration

Multidisciplinary group of investigators

Topics:

1. Identify molecular targets that are selectively expressed (or decreased) with inflammation
2. Create probes that target these molecules and which can be detected by functional MRI, CT, PET or Doppler scans
3. Validate these techniques in animal models of inflammation in various target organs

Application 4 page limit

Screened by Executive Committee

Reviewed and prioritized by External Advisory Committee

Pilot Projects ($50,000 each) – 1st year

1. **David Alcorta, Ph.D., Ron Falk, M.D., Charles Jennette (Depts. Medicine & Pathology)**

   Analysis of vascular inflammation using single photon emission computed tomography in a mouse model of ANCA – small vessel vasculitis

2. **Wenbin Lin, Ph.D., Rihe Liu, Ph.D., Weili Lin, Ph.D. (Depts. Chemistry, Pharmacy & Radiology**

   Early detection of vascular inflammation with functional magnetic resonance imaging contract agents

3. **Tim Nichols, M.D., Caterina Gallippi, Ph.D. (Depts. Medicine, Pathology, Biomolecular Engineering & Radiology)**

   Identification of molecular targets for noninvasive detection of inflammation in atherosclerosis in hypercholesterolemic/insulin resistant pigs

Pilot Projects – 1st year (continued)

4. **Balfour Sartor, M.D., J. Hansen, M.D., Ph.D., S. Tonkonogy, Ph.D., W. Lin, Ph.D., S. Aylward, Ph.D. (Depts. Medicine, Microbiology/Immunology, Computer Science, Radiology & Immunology – UNC-CH & NCSU – College of Veterinary Medicine)**

   Optimal molecular targets and MRI techniques to noninvasively evaluate experimental colitis

5. **Teresa Tarrant, M.D., Ph.D., D. Patel, M.D., Ph.D. (Depts. Of Medicine, Microbiology/Immunology)**

   Noninvasive imaging of inflammation in experimental arthritis

Pilot Projects/Core Facilities – 2nd year

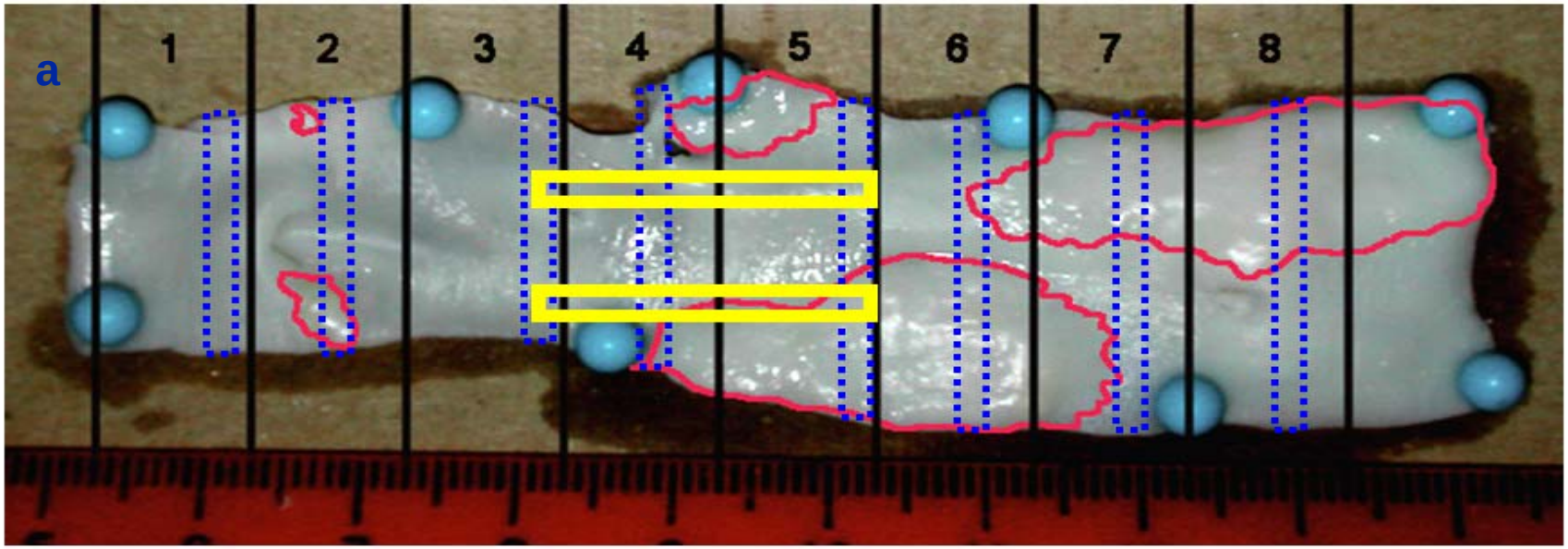
1. **Stephen Aylward, Ph.D. (Depts. Computer Science & Radiology)**

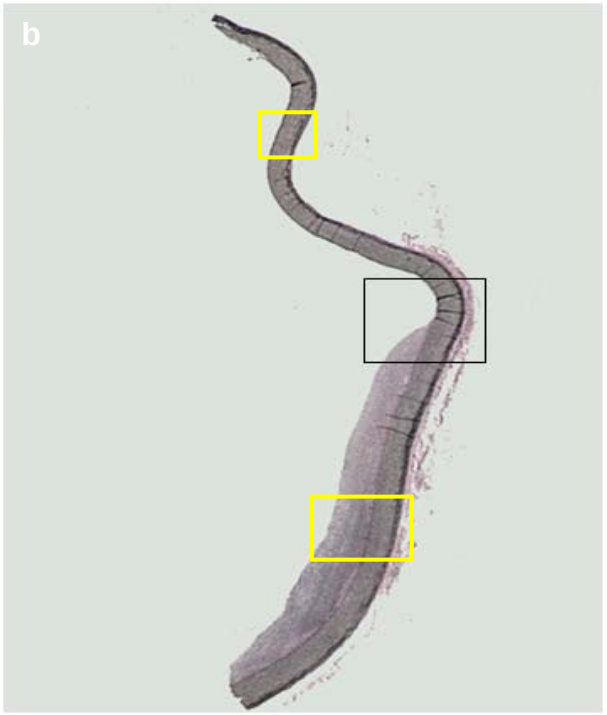
   Imaging Processing Core Facility
2. **Caterina Gallippi, Ph.D., T. Fischer, Ph.D., T. Nichols, M.D. (Depts. Biomolecular Engineering, Radiology, Medicine, Pathology)**

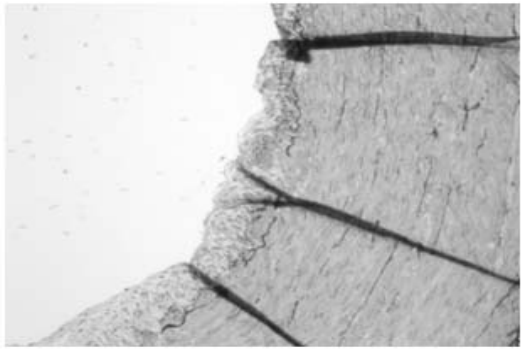
   Novel molecular ultrasound techniques for in vivo targeted imaging of vascular endothelial inflammation during arthrosclerosis in hypercholesterolemic/ insulin resistant pigs
3. **Weili Lin, Ph.D. (Dept. of Radiology)**

   Small animal cross sectional imaging core facility
4. **Joe DeSimone, Ph.D. (Dept. of Biomolecular Engineering)**

   Development of nanoprobes for MRI imaging

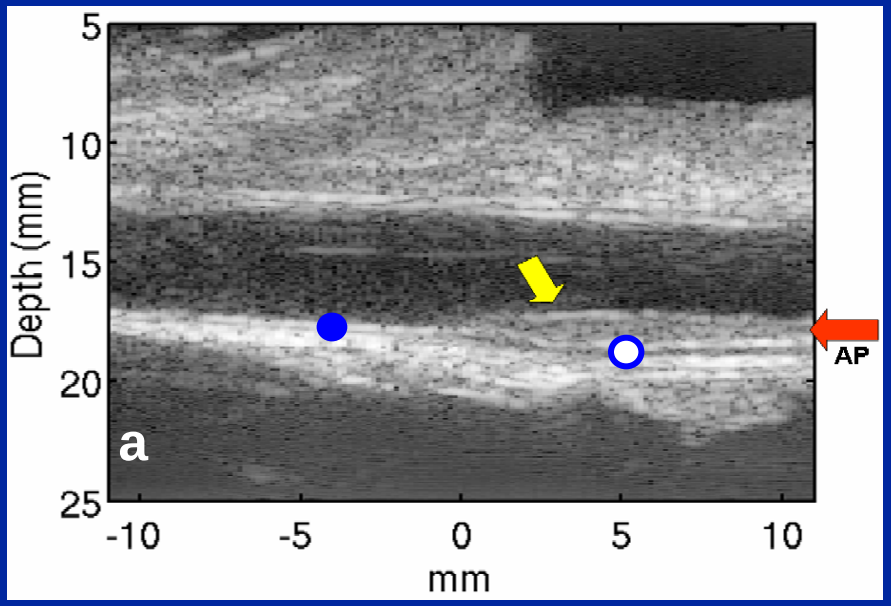


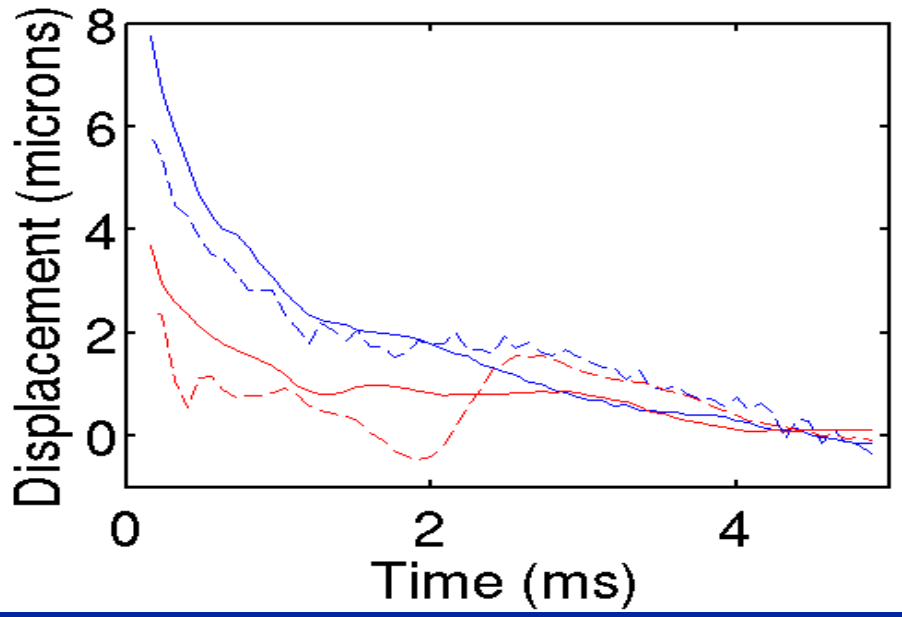


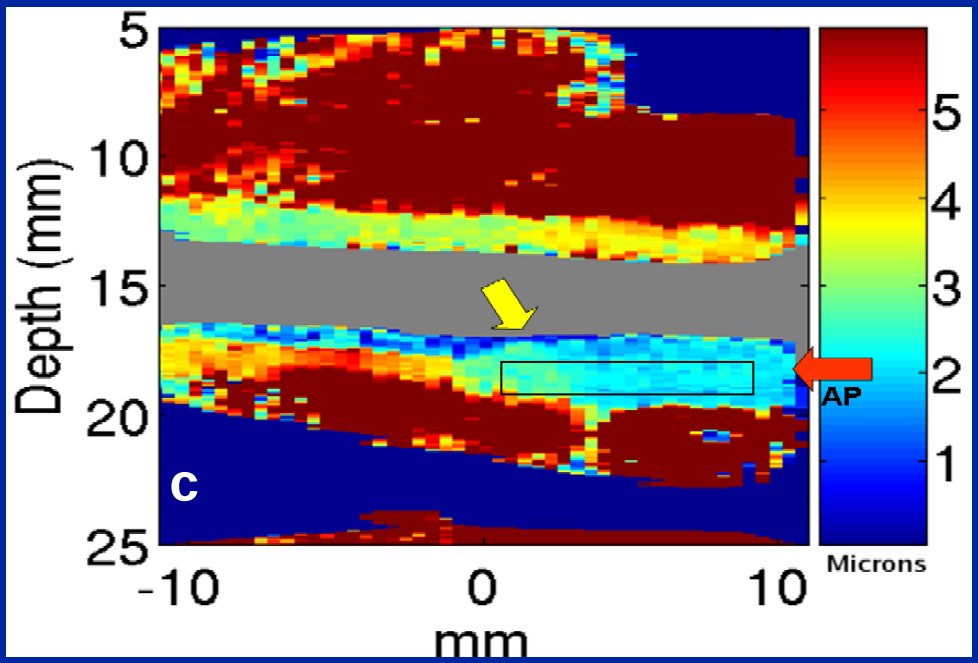


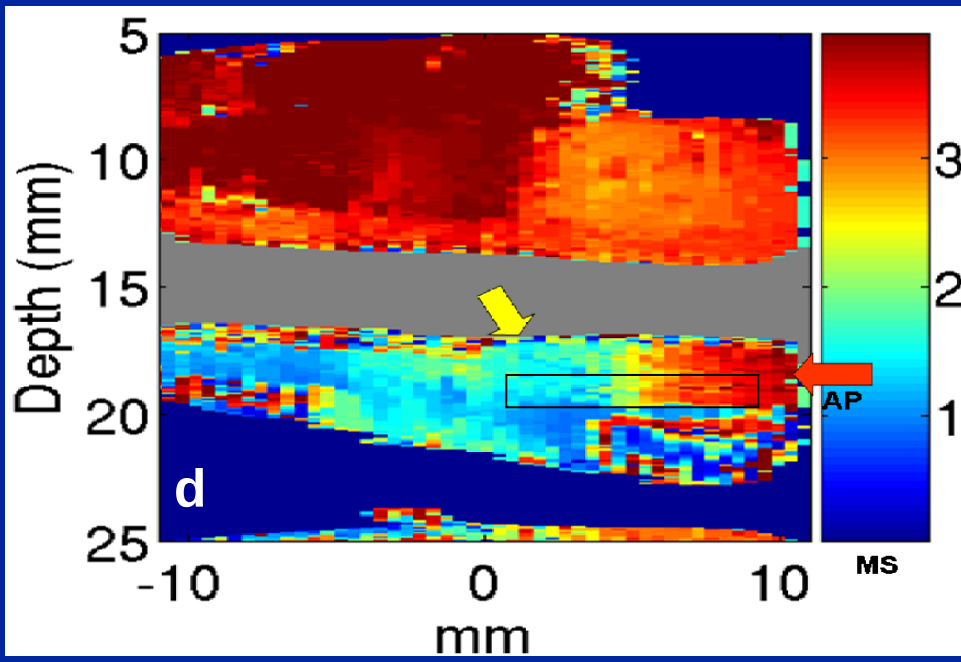
Atherosclerotic plaques in hypercholesterolemic pig model

Tim Nichols,
Caterina Gillippi



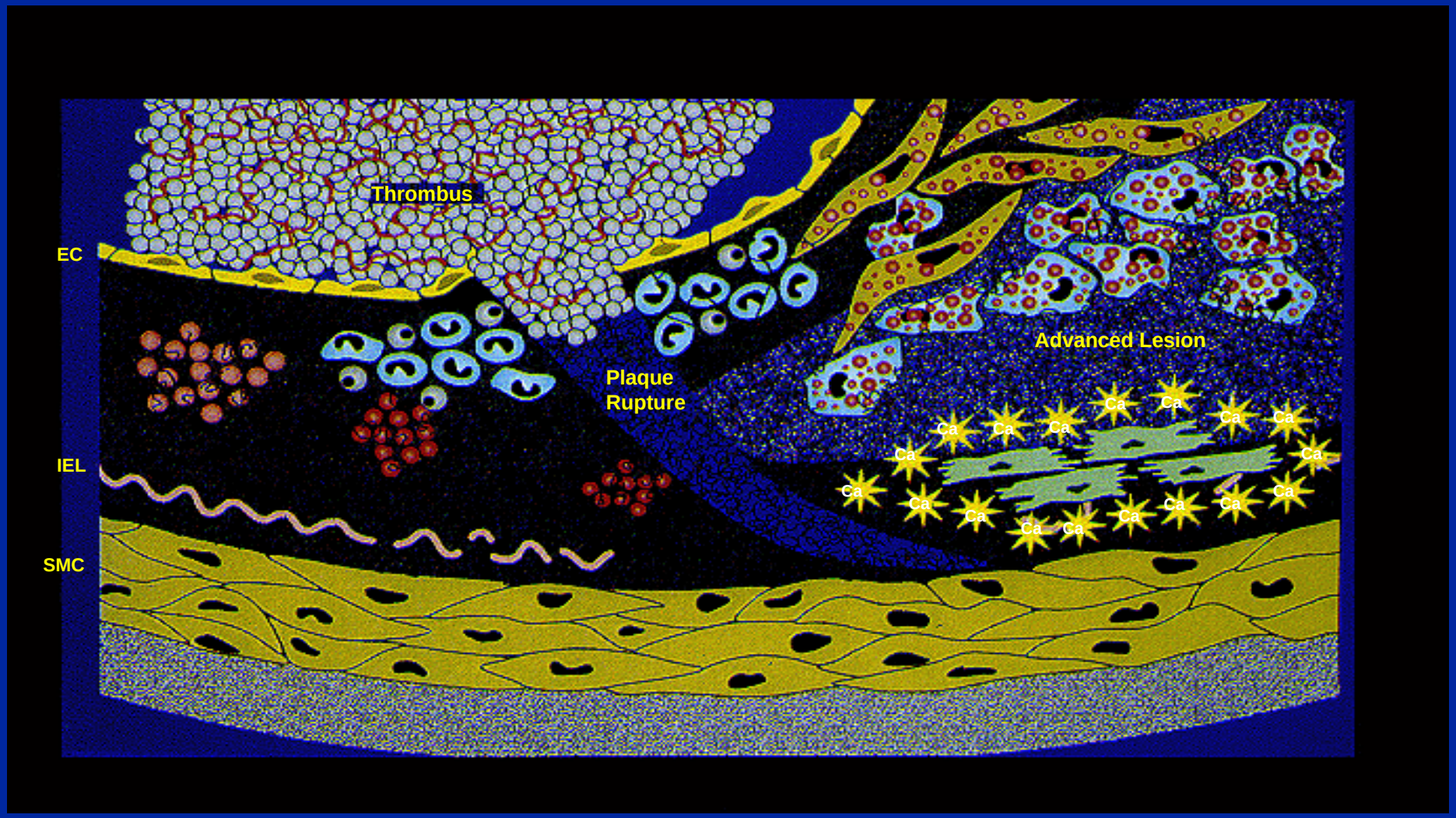






C. Gallippi et al

Thrombotic Atherosclerotic Plaque



Berliner et al. Atherosclerosis: Basic mechanisms. Oxidation, inflammation, and genetics. Circulation. 1995;91:2488-2496

Techniques to build a team

- No prior interactions among team members, but strong history of collaboration at UNC
- Team assembled around theme of inflammation, focus of noninvasive imaging agreed upon, members recruited based on expertise and interest
- Medical School Dean’s office supplied administrative support

Team building after funding

- Series of workshops to share expertise
- Work sessions by focus groups developed common dialogue
- Pilot studies awarded to multidisciplinary teams addressing relevant questions
- Monthly research in progress meetings to share expertise, accelerate research, promote interactions

Evaluation Techniques

- Monthly progress reports pilot studies
- Annual meeting external advisory committee (written suggestions)

Membership interaction and stability

- Growth of team with addition of expertise and announcement of meetings, pilot projects
- Interactions at workshops and research in progress meetings promote familiarity

Institutional Support

- Campus wide Roadmap Grant Office promotes investigator interactions, widespread distribution of information
- Pilot project funding considered in promotions

Management structure

- Multidisciplinary Executive Committee that meets monthly
- Democratic decisions